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First clinical experiences with rituximab in children with relapsed/refractory B-cell Acute Lymphoblastic Leukemia/Burkitt Lymphoma: report on 3 children treated on compassionate use basis

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Rituximab in three children with relapsed/refractory B-cell acute lymphoblastic leukaemia/Burkitt non-Hodgkin's lymphoma

Rituximab (Rituxan® or Mabthera®) is a genetically engineered chimaerical murine/human anti-CD20 monoclonal antibody. This B-cell marker is expressed in all cases of mature B-cell acute lymphoblastic leukaemia (B-ALL) and Burkitt-lymphoma, a high-grade B-cell non-Hodgkin's lymphoma (B-NHL) (Maloney *et al*, 1997; Patte *et al*, 2001).

Very few data are available regarding the treatment of children with B-ALL/NHL with rituximab (Corbacioglu *et al*, 2003), although the drug has been used for children with other indications, such as post-transplant lymphoproliferative disease and B-cell mediated autoimmune diseases, e.g. autoimmune haemolytic anaemia (Faye *et al*, 2001; Zecca *et al*, 2003).

We here report our experiences in three children with relapsed/refractory B-ALL/NHL who were treated with rituximab on compassionate use basis.

Patient 1 was a 4-year-old boy with B-NHL with bone marrow and central nervous system (CNS) involvement. Lymphadenopathy was found in mediastinal lymph nodes, liver, spleen, pancreas, as well as kidneys. He was treated according to the Lymphome Malins de Burkitt (LMB)-96 group C protocol. He recovered from two CNS relapses at 5 and 9 months after diagnosis, but 12 months after initial diagnosis, he developed a third relapse consisting of a tumour on the thoracic wall with a pleural effusion. A fine-needle aspirate showed B-NHL with CD20 positivity in >90% of the blasts. He was treated with rituximab 375 mg/m^2, and after the first infusion the thoracic wall tumour vanished. Three more infusions of rituximab (375 mg/m^2, once weekly) were given, after which a complete remission (CR) was established. No side effects of rituximab have occurred. After human leucocyte antigen (HLA)-identical bone marrow transplantation, he remained in CR for almost 5 years but died of progressive respiratory failure due to chronic graft *versus* host disease of the lungs.

Patient 2 was a 3-year-old boy diagnosed with B-ALL with CNS involvement. Two months after completing treatment according to the LMB-96 group C protocol, he developed a rapidly growing isolated testicular relapse. A biopsy showed that more than 95% of tumour cells were CD20 positive. He was treated with four infusions of rituximab 375 mg/m^2, which resulted in stable disease. Rituximab was well tolerated and no major side effects were observed in this patient. After additional chemotherapy the involved testis was surgically removed and autologous stem cell transplantation (SCT) was performed. Pathological examination of the removed testis showed no viable tumour cells. To date, he has been in CR for 4 years.

Patient 3 was a 9-year-old girl with B-NHL, showing bone marrow involvement and with localization of tumour in liver, spleen, both kidneys and synovia of right knee. The blasts were >90% CD20 positive. She was treated according to the LMB-96 protocol. She did not achieve CR, and developed CNS disease during treatment, as well as chemotherapy-resistant disease in the abdominal lymph nodes and liver. Re-induction was attempted with rituximab and repeated intrathecal triple therapy. After eight weekly infusions of rituximab (375 mg/m^2 once a week), CR was achieved. She was transplanted with an HLA-identical sibling donor. Unfortunately, shortly after SCT, a CNS relapse was diagnosed, without evidence of other localizations, after which she received palliative care and died from progressive CNS leukaemia. Rituximab does penetrate into the cerebrospinal fluid, be it at low levels of approximately 0·1% of serum levels, which may explain the occurrence of a subsequent CNS relapse without evidence for systemic disease that was seen in this patient (Rubenstein *et al*, 2003).

In conclusion, rituximab seems able to induce responses in children with relapsed/refractory mature B-ALL/NHL. Rituximab is generally well tolerated, apart from a 10% risk of infusion-related symptoms (Maloney *et al*, 1997). Further studies in children are needed to clearly establish the clinical efficacy and safety of rituximab in paediatric B-ALL/NHL and to investigate its role in combination chemotherapy.

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Endothelial cell activation and apoptosis in the thrombotic microangiopathies

We read with interest the recent report (Jimenez *et al*, 2003) that exposure of renal and cerebral microvascular endothelial cells (MVEC) to plasmas of patients with thrombotic thrombocytopenic purpura (TTP) leads to endothelial cell (EC) activation but not apoptosis. This distinction was based solely on changes in the ratio of CD62 to CD31 on released endothelial microparticles, but it supports earlier studies from these investigators utilizing terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling (TUNEL) (Jimenez *et al*, 2001). These findings are in contradistinction to the work of our group, demonstrating MVEC activation and apoptosis, as well as development of a procoagulant phenotype, following TTP plasma exposure *in vitro* (reviewed in Laurence & Mitra, 1997).

The authors have suggested that this difference may be due to divergent culture conditions, with our group pre-incubating cells in medium containing fetal bovine serum but devoid of human plasma or exogenous endothelial growth factors (Jimenez *et al*, 2001). This may indeed be the case, as we have noted that addition of normal plasma to such cultures blocks the apoptotic effect of TTP plasma, just as normal plasma infusions are therapeutic in most instances of clinical TTP (Laurence & Mitra, 1997). However, Jimenez and associates utilized an extracellular matrix (ECM) 'attachment factor' (Cell Systems, Kirkland, WA, USA), which may itself have anti-apoptotic properties for certain stimuli, given the close link between ECM composition and MVEC apoptosis *in vitro* and *in vivo* (Mauro *et al*, 2004).

Yet, a disagreement over the most appropriate conditions to unveil or amplify an apoptotic and/or activation-inducing effect with TTP plasma – after all, cell culture itself perturbs EC from a quiescent *in vivo* state to an activated phenotype (Cines *et al*, 1998) – should not obfuscate the fact that EC apoptosis has been demonstrated in involved tissues of TTP patients utilizing TUNEL assays and morphology, together with detection of EC circulating in the periphery, presumably representing apoptotic or otherwise injured EC detached from the underlying ECM (reviewed in Dang *et al*, 1999). Our *in vitro* assays also reproduce the EC tissue lineage distinction found *in vivo* in TTP, including lack of pathology in